Remarks

The Interview

The Applicants Gerianne DiPiano, Dr. Peter Mays and Dr. John Zimniak, representing the licensee FemmePharma, and the undersigned Patrea Pabst and Adam Raymond greatly appreciated the opportunity to meet with Examiners Kim and Fetterolf to discuss the present application on February 2, 2010, at U.S. Patent Office. During the interview, the FemmePharma representatives discussed the background of the company in developing women's products, the product in clinical trials (danazol formulated in a hydroalcoholic gel with a transdermal penetration enhancer that solubilizes the water-insoluble danazol so that it can penetrate the skin into the underlying breast tissue), the long standing need for the transdermal danazol product in treating breast disease without any systemic side effects, and the lack of any previous danazol transdermal product. Enclosed is a copy of the Power Point presentation that was provided to the examiner. Also enclosed are the undersigned's highly condensed notes from the oral presentations made by Ms. DiPianno and Dr. Zemniak. Dr. Mays offered to review the clinical trial results in detail, as well as why the formulation was developed and how the results were surprising with respect to the selection of (1) a hydroalcholic gel in combination with (2) N-methyl-2-pyrrolidone or 2-pyrrolidone.

As discussed at the interview, in view of the imminent approval of the drug by the Food and Drug Adminsitration, to facilitate prosecution, it was agreed to limit the drug formulation to a hydroalcholic gel (page 8, line 11) comprising danazol and N-methyl-2-pyrrolidone or 2-

pyrrolidone (page 9, lines 6 and 7), which both solublizes danazol and improves its delivery across the skin to the underlying breast tissue, so that the claims are commensurate in scope with the previously submitted declaration. It was agreed that the claim amendments were supported by these references to the specification.

Claims 1 and 10 have been amended to limit the drug to danazol and incorporate the limitations of claims 2 and 4, and specify that the carrier is a hydroalcoholic gel. The transdermal penetration enhancer is limited to N-methyl-2-pyrrolidone or 2-pyrrolidone. Support is found at page 9, lines 6 and 7. Claims 1 and 10 have also been amended to specify the formulation should deliver the drug across the stratum corneum to the underlying breast tissue. Support for this amendment can be found throughout the specification on page 7, lines 3 through 5, and page 7, line 27 through page 8, line 11. This is achieved in part by the penetration enhancer being able to solubilize the danazol. Support is found at page 6, lines 3 and 4, and page 7, line 26, to page 8, line 11.

Claim 10 has been further amended to specify that the method is for use in treatment of a disease or disorder of the breast treatable with danazol. Support can be found from page 1, lines 12 through page 3, line 15.

Claim 17 has been amended to limit the benign diseases of the breast to those treatable with danazol. Claims 2-5, 7, 8, 11, 12, 14, and 15 have been cancelled.

Rejection Under 35 U.S.C. § 103

Claim 1 was rejected under 35 U.S.C. § 103(a) as obvious over US 2003/0153585 to Schreder in view of U.S. Patent No. 5,993,856 to Ragavan ("Ragavan 1"). Applicants respectfully traverse this rejection.

The Legal Standard

The starting point for any such analysis must be the Supreme Court's decision in *KSR*, which refocuses the determination of whether a claimed invention is obvious back to the process the Court had defined in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). There, the Court had held that the obviousness determination should address four factors, all of which must be considered, though not in any prescribed order: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need. *Id.* The Court cautioned that the fact finder should be careful about reading the teachings of the invention at issue into the prior art, to avoid applying inappropriate hindsight, *ex post* reasoning. *Id.* at 36.

Analysis

(a) The scope of the prior art

US 2003/0153585 to Schreder

US 2003/0153585 A1 describes pharmaceutical preparations containing 2-pyrrolidone as a solubilizer for oral administration [0001, Claim 8). Schreder incorporates prior art on the use of 2-pyrrolidone, in combination with a promoter, to improve the ability of active benzodiazepines to permeate through the skin to achieve pronounced systemic concentration and therefore systemic efficacy [0039]. Schreder also utilizes 2-pyrrolidone as an excipient to be employed in ointments or gel-like medicament forms which can be applied to mucous membranes [0045]. Mucous membranes implies application to the oral, nasal, vaginal and rectal cavities, not dermal application. The specific examples cited, the experimental and statistical procedures used, and frequent mention of terminology relative to oral absorption (gastric, fasted vs. fed, dissolution etc) are all evidence that the formulations were intended solely for oral administration and not regional dermal delivery. There are no examples of a topical ointment. gel or other means for regional delivery of agents to the underlying tissue beneath the skin. The specific intent was to increase the oral absorption of poorly soluble agents to achieve high systemic levels as judged by their use of AUC calculations and determination of absolute bioavailability.

U.S. Patent No. 5,993,856 to Ragavan ("Ragavan 1")

Ragavan 1 discloses formulations for topical or local delivery on reproductive organs to achieve relatively highly high blood levels in the regions to be treated in the substantial absence of systemic levels which might cause side effects. Ravagan 1 does not disclose the use of a hydroalcoholic carrier in combination with N-methyl-2-pyrrolidone or 2-pyrrolidone to

solubilize danazol and increase flux across the skin to the breast. The formulations of Ragavan 1 are intended for delivery across the mucosal membranes, which does not present the difficulty associated with delivery of the drug through the skin.

(b) Ascertaining differences between the prior art and the claims

The claims are drawn to a composition and method of use thereof for the topical application of a danazol gel containing 2-pyrrolidone to produce low to negligible systemic blood concentration but sufficient tissue levels to be clinically efficacious. The Schreder application actually confirms the novelty of the claimed formulations and methods of use. The claims are not drawn to the oral use of a danazol formulation containing 2-pyrrolidone. The claimed formulation uses 2-pyrrolidone as a solubilizer and penetration enhancer to deliver danazol across the skin (stratum corneum) to the underlying breast tissue to treat a disease of the breast with minimal systemic exposure as gauged by circulating levels of the drug in the serum (see Mays affidavit from August 2009). It is the local/regional delivery of danazol to the breast to relieve breast pain associated with fibrocystic breast disease, with minimal systemic exposure, thereby reducing systemic androgenic side-effects of danazol that is novel and non-obvious.

Ravagan does not make up for these deficiencies. Ragavan does not illustrate a danazol formulation formulated with a hydroalcoholic carrier including a transdermal penetration enhancer, the formulation providing relief from disease or disorders of the breast and the property of the carrier *capable of delivering the drug to the breast tissue* and to promote delivery of the drug across the stratum corneum with low serum drug levels compared to the systemic

administration of the drug (Office Action mailed September 30, 2009, bottom of page 5 to top of page 6).

The Examiner suggested that one of ordinary skill in the art would recognize the disclosure of polyvinylpyrrolidone (PVP) as an excipient in Ravagan 1 as the penetration enhancer of the present claims. Without making any admissions, and solely to facilitate prosecution of the application, Applicants further amended the claims to limit the transdermal penetration enhancer to N-methyl-2-pyrrolidone or 2-pyrrolidone. As discussed in the interview, and in the Declaration under C.F.R. 1.132 of Dr. Peter Mays, submitted with the Amendment and Response filed August 31, 2009, N-methyl-2-pyrrolidone or 2-pyrrolidone in combination with a hydroalcoholic gel acts as both a solubilizer for danazol ***and*** as a transdermal penetration enhancer, increasing flux across the skin. Most of the prior art discloses formulations where the danazol is in microparticulate form, not solubilized. The microparticulate danazol will not penetrate the skin. This is obviated by the claimed formulation where the transdermal penetration enhancer is selected to solubilize the danazol. This produces results that are neither anticipated by, nor could have been predicted from, the prior art. In particular, the prior art only discloses the use of a material such as polyvinylpyrrolidone ("PVP") in combination with a hydrogel excipient.

As Dr. Mays states in paragraphs 18 and 19:

18. In the PEG ointment #1 15% pyrrolidone did not enhance danazol flux (0.004 μg/cm^2/hr), whereas in hydroalcoholic gel # 2 15% pyrrolidone in the presence

of 47% alcohol enhanced the danazol flux rate (0.127 μg/cm^2/hr), a rate of flux twice that seen with oleyl alcohol alone (Exhibit 5, page 5, Table 2). This finding was unexpected.

19. The combination of Danazol + Gel + Alcohol + PVP is not relevant to this application, as PVP, a known penetration enhancer, is a polymer which confers different physicochemical properties to the formulation than 2-pyrrolidone, which is a low molecular weight small molecule. Within the formulation of hydroalcoholic gel #2, the 2-pyrrolidone acts as both a solubilizer for danazol and a penetration enhancer.

For at least these reasons, PVP is insufficient as a component of the danzol formulation of the present application.

(c) Secondary consideration of non-obviousness

The court has held that any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need, should also be considered. As presented by Applicants during the interview, more than 26 million women in the United States suffer from fibrocystic breast disease. Traditional treatments, including oral danazol therapy, cause significant undesirable side effects. Only Applicants have developed a transdermal formulation that successfully delivers danazol across the breast skin to the underlying breast tissue, providing relief from benign diseases or disorders of the breast, without achieving systemically significant levels, or the associated side-effects. The claimed formulation

overcomes the failure by others and provides a solution to the long standing but unmet need for treatment of breast pain in the substantial absence of side effects.

The declaration provides unexpected results. Applicants demonstrated that the claimed formulation including both a hydroalcoholic gel carrier and N-methyl-2-pyrrolidone or 2-pyrrolidone is more effective than other danazol formulations. As described in the declaration, a transvaginal formulation was ineffective in penetrating the skin (paragraphs 7 through 9). Although a transdermal formulation containing danazol, propylene glycol and oleyl alcohol did penetrate the skin, the flux was lower than when the formulation included a 2-pyrrolidone (0.055 $\mu g/cm^2/hr$) (Statement 13, and Exhibit 3, page 5, Table 2). The penetration enhancer 2-pyrrolidone was added to various formulations to improve the rate of flux, and formulations were tested for their ability to improve flux. 15% pyrrolidone did not enhance danazol flux (0.004 $\mu g/cm^2/hr$) in the PEG ointment (i.e., a non-alcoholic carrier). In contrast, 15% pyrrolidone in the presence of 47% alcohol enhanced the danazol flux rate (0.127 $\mu g/cm^2/hr$) of hydroalcoholic gel # 2, a rate of flux twice that seen with oleyl alcohol alone (Exhibit 5, page 5, Table 2). These findings were unexpected. As discussed above, 2-pyrrolidone in combination with a hydroalcoholic gel acts as both a solubilizer for danazol *and* as a transdermal penetration enhancer, increasing flux across the skin. The data in the declaration is commensurate in scope with the claims as amended. The claims are now limited to a danazol formulation including a hydroalcoholic gel carrier and N-methyl-2-pyrrolidone or 2-pyrrolidone. The comparative data

of the declaration describes the same formulation containing a hydroalcoholic gel carrier and 2-pyrrolidone.

Rejoinder and allowance of all claims 1, 10, 17, and 19 is respectfully solicited.

Respectfully submitted,

/Patrea L. Pabst/
Patrea L. Pabst
Reg. No. 31,284

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PABST PATENT GROUP LLP
1545 Peachtree Street, NE
Suite 320
Atlanta, Georgia 30309
(404) 879-2151
(404) 879-2160 (Facsimile)